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Prenatal Exposure to Polychlorinated Biphenyls (PCB) and Dichlorodiphenyldichloroethylene (DDE) and Birth Weight: A Meta-analysis within 12 European Birth Cohorts

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Competing financial interests

None declared

List of abbreviations

BMI	bodymass index, weight(kg) /height(cm)*height(cm)
DDE	dichlorodiphenyldichloroethylene
DDT	dichlorodiphenyltrichloroethane
ENRIECO	ENvironmental health RIsks in European birth Cohorts
ER	estrogen receptor
FT4	free thyroxine
LOD	limit of detection
LOQ	limit of quantification
OBELIX	OBesogenic Endocrine disrupting chemicals: LInking prenatal eXposure to the development of obesity later in life)
NDL-PCB	non-dioxinlike polychlorinated biphenyl
PCB	polychlorinated biphenyl
POC	persistent organochlorine
PUFA	n-3 polyunsaturated fatty acids
TSH	thyroid-stimulating hormone

ABSTRACT

Objectives Exposure to high concentrations of persistent organochlorines may cause fetal toxicity, but the evidence at low exposure levels is limited. Large studies with substantial exposure contrasts and appropriate exposure assessment are warranted. Within the framework of the EU ENRIECO and EU OBELIX projects, we examined the hypothesis that polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE) adversely affects birth weight.

Methods We used maternal and cord blood and breast milk samples in 7,990 women enrolled in 15 study populations from 12 European birth cohorts from 1990-2008. Using identical variable definitions, we performed for each cohort linear regression of birth weight on estimates of cord serum concentration of PCB 153 and p,p'-DDE adjusted for gestational age and *a priori* selected covariates. We obtained summary estimates by meta-analysis and performed analyses of interactions.

Results The median concentration of cord serum PCB 153 was 140 ng/L (range of cohort medians 20–484) and that of p,p'-DDE was 528 ng/L (range of cohort medians 50–1208). Birth weight decreased with increasing cord serum concentration of PCB 153 after adjustment for potential confounders in 12 of 15 study populations. The meta-analysis including all cohorts indicated a birth weight decline of 150 g (95% CI -250, -50) per 1-µg/L increase in PCB 153, an exposure contrast that is close to the range of exposuress across the cohorts. A 1-µg/L increase in p,p'-DDE was associated with a 7 g decrease in birth weight (95% CI -18, 4 g).

Conclusions The findings suggest that low-level exposure to PCB (or correlated exposures) impairs fetal growth, while p,p'-DDE exposure does not. The study adds to mounting evidence that low-level exposure to PCBs is inversely associated with fetal growth.

INTRODUCTION

From the 1930s polychlorinated biphenyls (PCBs) have been manufactured in large quantities for use in many industrial applications until they were banned in most countries in the 1970s. Dichlorodiphenyltrichloroethane (DDT) is a pesticide that since the 1940s has been used worldwide for malaria vector control, and it is still in use in some areas (Aneck-Hahn et al. 2007; Ayotte et al. 2001). PCBs and the main DDT metabolite dichlorodiphenyldichloroethylene (p, p'-DDE) bioaccumulate in fat tissues, biomagnify through the food chain, are highly persistent in living organisms and comprise the bulk of organochlorine residues in human tissues (Longnecker et al. 2003). The concentrations of these chemicals in blood, fat, and milk have decreased over the past 30 years but are still detectable in blood of the general population all over the globe (Jonsson et al. 2005). It has been suggested that organochlorines may interfere with fetal growth through interaction with endogenous steroid hormone signaling (Faroon and Olson 2000; Lopez-Espinosa et al. 2009). Birth weight restriction related to PCBs was first described in humans after the 1968 Yusho incident in Japan, where thousands of pregnant women were intoxicated by PCB-contaminated cooking rice oil (Yamashita and Hayashi 1985). During the past 15 years several additional studies have addressed human reproductive toxicity of PCBs by studies of fishing communities, fish eaters and the general population in various regions, as reviewed by Toft et al. (Toft et al. 2004) and Longnecker et al. (Longnecker et al. 2003). Findings from these studies on the relation between maternal PCB exposure and birth weight are not consistent – some indicating an inverse association (Fein et al. 1984; Karmaus and Zhu 2004;Murphy et al. 2010; Patandin et al. 1998; Rylander et al. 1995; Rylander et al. 1996; Rylander et al. 1998; Wojtyniak et al. 2010), an inverse association among male infants only (Sonneborn et al. 2008), a positive association (Dar et al. 1992) or no association at all (Gladen et al. 2003;Grandjean et al. 2001;Longnecker et al. 2005;Mendez et al. 2010;Vartiainen et al. 1998).

A large US study of women giving birth between 1959 and 1966 (when DDT was still being used) found a dose-response relationship between DDE-concentration in maternal serum and

low birth weight (Longnecker et al. 2001). Children in the high exposure group (> 60 ng/g) weighed 150 g less and were born about one week earlier than the children in the low exposure group (< 15 ng/g). Similar results were observed in an Indian study of pregnant women with high DDT exposures (Siddiqui et al. 2003) but serum DDT and/or DDE was not associated with birth weight in two other studies (Gladen et al. 2003;Wojtyniak et al. 2010).

Many factors may contribute to the discrepant findings in earlier observational studies of reproductive effects of PCBs. This includes correlations in some populations between persistent organochlorines (POCs) and dietary nutrients as n-3 fatty acids that may increase gestational age (Grandjean et al. 2001), limited study size, insufficient exposure levels or contrasts between compared populations (Wojtyniak et al. 2010), exposure to different mixtures of PCB congeners (Murphy et al. 2010), confounding by other organochlorines such as HCB (Eggesbo et al. 2009) and different susceptibility of studied populations (Sonneborn et al. 2008). Publication bias could also be a problem with studies not finding an association being underreported.

A recent review concluded that large scale-studies with a sufficient number of participants in well-defined groups with substantial exposure contrast are needed in order to further elucidate the possible adverse effects of POCs on human reproductive health (Toft et al. 2004). The ENRIECO (Enrieco - ENvironmental Health RIsks in European birth COhorts 2009) framework of European birth cohorts and the cohorts included in the EU OBELIX (OBELIX - OBesogenic Endocrine disrupting chemicals: LInking prenatal eXposure to the development of obesity later in life 2009) project provide the basis for such a study.

The objective of this study was to examine associations between biological markers of exposure to POCs and birth weight in 12 European birth cohorts, including possible modifying effects of gender and tobacco smoking.

METHODS

Description of the cohorts

The ENRIECO project has provided an inventory of European birth cohorts aiming at investigating the impact of environmental exposures on health in pregnancy and early childhood. Among these cohorts, we identified 14 cohorts of pregnant women with individual measurements of PCB 153 and p,p'-DDE. One invited cohort declined participation for reasons not related to current hypotheses, and we excluded one cohort that used placenta tissue samples for exposure assessment [the Finish LUKAS cohort (Karvonen et al 2009)]). Each cohort targeted the general population and included births from 1990 to 2008. We divided the INMA cohort into two populations based upon the matrix used for POC measurements (maternal serum or cord serum) and divided the INUENDO cohort into three populations (Greenland, Warsaw, and Kharkiv) resulting in 15 study populations with a total of 7,990 live born singletons with PCB 153 measurements and 7,788 live born singletons with p,p'-DDE measurements (Table 1). The concentrations of PCBs and p,p'-DDE were analyzed in maternal serum or whole blood collected during pregnancy (seven populations), cord serum or plasma (five populations) or breast milk (three populations). Detailed information regarding the study cohorts are provided in Table 1 and Supplemental Material, Table 1.

Exposure assessment

Analysis of PCB 153 and p,p'-DDE

We used PCB 153 as biomarker of PCB exposure because concentrations of this PCB congener are relatively high and highly correlated with the total molar concentration of PCBs (Glynn et al. 2000;Muckle et al. 2001;Needham et al. 2011a). The elimination half-life of PCB-153 is more than ten years (Ritter et al. 2011) and that of p,p'-DDE, the major metabolite of DDT, is approximately 5 years (Ferreira CP et al 2011).

In order to facilitate comparisons of results from cohorts using different matrices for exposure assessment, we expressed all contaminant levels as wet weight cord serum levels,

which directly reflect fetal exposure at the time of delivery (some compounds do not cross the placenta efficiently). For populations that did not have cord blood analyses, we estimated concentrations in cord serum from the concentrations measured in maternal serum (FAROES2, INMA, INUENDO, and RHEA), maternal whole blood (DUISBURG), or breast milk (FAROES3, HUMIS, and ELFE pilot), using the following conversion factors (see Supplemental Material, pages 2-3 for details)

cord serum level (ng/L) = 0.20 * maternal serum level (ng/L)

cord serum level (ng/L) = 1.20 * breast milk level (ng/g fat)

cord serum level (ng/L) = 0.36 * maternal whole blood level (ng/L)

We compiled information about chemical-analytical methods and their detection limits (see Supplemental Material, Table 2). High quality analytical data were available for both PCB 153 and p,p´-DDE in each cohort except the GRD and ELFE pilot cohorts, where only PCB 153 was measured. Spearman correlation coefficients between PCB 153 and p,p'-DDE in the cohorts ranged from 0.3 to almost 1, with a median of 0.6.

Outcome variable and covariates/confounders

The outcome of interest was birth weight, which was extracted from medical records. Covariate data were obtained from questionnaires and medical record information for children and their mothers, including information from antenatal health care visits. Gestational age was estimated from the date of the last menstrual period and/or by ultrasound. For five study populations, the data obtained from the last menstrual period were replaced by ultrasound determination if the discrepancy between the two techniques exceeded 7-14 days (see Supplemental Material, Table 1). All participants completed an extensive questionnaire themselves or by a telephone or face-to-face interview, assessing information on lifestyle, diet, use of tobacco and alcohol, residence history, health, education, hobbies, and occupation (if applicable). Each study was approved by appropriate national ethical committees and mothers provided written informed consent for participation.

Statistical analysis

We developed a uniform script in SAS version 9.1 (SAS Institute Inc., Cary, NC, USA) and SPSS versions 17.0 and 18.0 (SPSS, Chicago, IL) to define the variables, units and categories used in statistical analyses for each of the 11 study centres. We allowed cohort specific variables for region and socioeconomic status. For some important confounders, missing values were replaced by the most frequent outcome for the study population. Specifically, missing data for smoking and alcohol consumption were replaced by non-smoking/ non-drinker, except for Greenland where mothers with missing data for smoking were assumed to be smokers, and Warsaw, where mothers with missing data for alcohol were assumed to be moderate drinkers. For continuous variables (e.g., maternal height) missing values were replaced with the population-specific median.

In all 15 study populations PCB 153 and p,p'-DDE were detected in at least 78% of subjects, and in 11 populations both compounds were detected in more than 95% of samples (Table 2). We replaced values below the limit of detection (LOD) or quantification (LOQ) by the LOD or LOQ divided by the square root of two (Hornung and Reed 1990).

We developed separate multiple linear regression models to estimate the association between birth weight and PCB 153 or p,p'-DDE concentrations in cord serum. Several known determinants of birth weight were included in the models regardless of actual degree of confounding of the POC-birth weight association in the individual cohorts (Bailey and Byrom 2007;Goldenberg et al. 1997). These included gestational age (weeks, linear and quadratic terms), offspring gender (male/female), region (cohort-specific categories), maternal BMI (4 categories: <18.5 kg/m², 18.5-<25 kg/m², 25-<30 kg/m² and >=30 kg/m²), height (continuous), smoking status during pregnancy (3 categories: non-smoking, smoking <=9 cigarettes/day, smoking >9 cigarettes/day), socioeconomic status (cohort-specific categories), mother's age (4 categories: <25 years, 25-29 years, 30-34 years and =35 years), parity (3 categories: 0, 1 and =2), ethnicity (cohort-specific categories), and gestational age at time of sampling (4 categories: first, second, third trimester and postnatal). We evaluated

gender and smoking status as potential effect modifiers based on literature regarding PCB exposure and growth or development (Hertz-Picciotto et al. 2005;Verhulst et al. 2009) and we also examined interaction between PCB 153 and p,p'-DDE. Effect modification (interaction) was analyzed in models including main effects and cross-product terms. A p-value less than 0,05 for the effect of the cross-product was taken as an indication of interaction. Finally, we examined associations of gestational age with PCB 153 and p,p'-DDE in cord serum by linear regression to determine if associations with birth weight might be mediated by effects on gestational age.

We checked assumptions of normality, constancy of variance, independence (randomness), and linearity with informal diagnostic plots and formal tests [White's General test for constancy of variance (White 1980), Kolmogorov-Smirnov test for normality, and the lack of fit test for linearity (Neter et al. 1996)] and fitted regression models with and without influential outliers.

We used meta-analyses to estimate the overall summary effects of levels of PCB 153 and p,p'-DDE in cord serum on birth weight using R version 2.11.0 (R Foundation for Statistical Computing, Vienna, Austria) First, we tested for heterogeneity between effect estimates using the Q test (Cochran 1954). If the result of the Q test was statistically significant (p-value < 0.05), an indication of heterogeneity across populations, we used random effects analyses (DerSimonian and Laird 1986). In addition, because the Q test has low statistical power with few studies (Hardy and Thompson 1998), we also used the I^2 to assess heterogeneity (Higgins and Thompson 2002). Following the thresholds provided by Deeks et al. (Deeks et al. 2008), we interpreted an $I^2 > 30\%$ as reflecting at least moderate heterogeneity. Therefore, when the Q test was not statistically significant, but the $I^2 > 30\%$ we also used a random effects model. Using this approach we observed significant heterogeneity across study populations for the PCB-153 association (P=0.01) and therefore

we used a random effects model for all analyses. Summary estimates were weighted by the inverse variance of each cohort. To determine the influence of any particular population, we repeated the meta-analyses leaving one population out at the time.

RESULTS

The median birth weight ranged from 3210 to 3750 g, and median gestational age from 38 to 40 weeks. The proportion of Caesarian sections was below 25% in all populations except RHEA (43.3%) (see Supplemental Material, Table 1). In five populations more than 20% of mothers were less than 25 years of age at delivery and in two populations more than 20% were above 35 years of age. The proportion of nulliparous women exceeded 40% in nine of the populations.

The median concentration of PCB 153 in cord serum in the 15 study populations ranged from 20 to 484 ng/L (Table 2 and Supplemental Material, Figure 1). The median cord serum PCB 153 concentration in the Faroese population was 3.4 times higher than the overall median of 140 ng/L. The populations with the lowest median PCB 153 concentrations in cord serum (e.g. Warsaw, Kharkiv, HUMIS, and RHEA) also had a narrow range of concentrations compared with the other populations (range from P10 to P90: 7 to 83 ng/L compared with 14 to 1302 ng/L).

The median level of p,p'-DDE in cord serum in the 15 populations ranged from 50 to 1208 ng/L (Table 2 and Supplemental Material Figure 2). The median cord serum p,p'-DDE concentration in the Faroese population was 2.2 times higher than the overall median of 528 ng/L.

Gestational ages ranged from 25 – 44 weeks (see Supplemental Material, Table 1). Associations between POC concentrations and gestational age, including preterm births, were

not statistically significant for any of the individual populations (data not shown) or in the meta-analysis (â = 6.2 * 10^{-6} (95% CI: -2.5 * 10^{-5}; 3.7 * 10^{-5}) and p=0.18 for PCB 153 and â = -1.2 10^{-5} (95% CI: -4.8 * 10^{-5}; 2.5 * 10^{-5}) and p=0.40 for p,p'-DDE).

There was a statistically significant inverse association between PCB 153 concentrations in cord serum and birth weight in four populations (GRD, INMA cord, FLEHSI, and Greenland) (Figure 1).

The meta-analysis showed a statistically significant inverse association between PCB 153 concentrations in cord serum and birth weight, corresponding to a 150 (95% CI: -240; -50) gram reduction per 1-µg/L increase in cord serum PCB 153 (Figure 1). A sensitivity analysis restricted to 3,856 nulliparous women produced a combined estimate of similar magnitude (â = -152 g/µg PCB 153 (95% CI: -341; 37), and p=0.12; see Supplemental Material, Table 3). Analyses leaving out one population at the time did not show qualitatively different results from those reported (data not shown). In the meta-regression, biological sample matrix (cord serum, maternal blood/serum, or milk), time period (1990-1999/2000-2008), geographical area (FAROES2, FAROES3, Greenland and HUMIS versus other cohorts), and fish consumption (FAROES2, FAROES3 and Greenland versus other cohorts were not significant predictors of heterogeneity among the study populations (data not shown). Separate meta-analytic regressions by sample matrix were consistent with the overall combined estimate for maternal serum (â = -120 g/µg PCB 143 (95% CI: -260; 10)), stronger for the combined estimate for cord serum (â = -290 g/µg PCB 143 (95% CI: -540; -40)) and weaker for breast milk (â = -50 g/µg PCB 143 (95% CI: -160; 50)).

The meta-analysis of the relation between cord serum p,p'-DDE and birth weight (Figure 2) did not indicate a statistically significant association [7 g reduction per 1-µg/L increased in cord serum p,p'-DDE (95% CI: -18, 4)]. Analyses leaving one cohort out at the time did not show qualitatively different results. Separate meta-analytic regressions by sample matrix were consistent with the overall result and did not show an association between p,p'-DDE and birth weight (data not shown).

Associations of birth weight with PCB 153 and p,p'-DDE were not modified by gender or smoking (data not shown). Associations were also comparable when lipid-adjusted POC concentrations were modeled and when exposures were modeled using quadratic and log-linear transformation (data not shown). The expected associations between birth weight and gender (higher birth weight for males compared to females), tobacco smoking (smoking during pregnancy leading to lower birth weight) and body mass index (mothers with a high BMI have babies with higher birth weights) were demonstrated in all cohorts (data not shown). A sensitivity analysis restricted to infants born at term (e.g. gestational age between 37 and 42 weeks) showed no material changes in effect estimates (data not shown). When adjusting for p,p'-DDE in the models, the inverse association between PCB 153 and birth weight was not altered and no significant interaction was found between PCB 153 and p,p'-DDE on birth weight within the cohorts (data not shown).

DISCUSSION

In our meta-analysis of 12 European birth cohorts (15 study populations) we observed decreases in birth weight independent of gestational age with increasing fetal PCB 153 concentrations. Across all cohorts birth weight declined by 150 g in association with a 1-µg/L increase of PCB 153 in cord serum, an exposure contrast that is close to the range of exposure levels across the cohorts. The magnitude of this association is comparable to the association between birth weight and smoking about 10 cigarettes per day during pregnancy, and more pronounced than the association with exposure to environmental tobacco smoking, which according to a review of several earlier studies and meta-analyses confer an average reduction in birth weight of 30-40 g(Lindbohm et al. 2002). If the observed associations are causal, effects attributable to PCB exposure may be clinically relevant in the studied populations.

In contrast, we found no indications that fetal exposure to the DDT metabolite p,p'-DDE was related to birth weight, which is consistent with results of a large study based upon the US Collaborative Perinatal Project (Longnecker et al. 2001) that examined children born from 1959-1966 before DDT was banned in US. Although results of the CPP study strongly suggested that DDT exposure was related to preterm birth and small for gestational age babies, no association was detected with maternal serum concentrations below 10 µg/L (corresponding to a concentration of 2.5 µg/L in cord serum), which is higher than DDE concentrations in more than 95% of pregnant women participating in our study (Supplemental Material, Figure 2).

Fish is an important source of PCB exposure in communities with a high seafood intake (Thorsdottir et al. 2004), but fish meals also contribute substantially to internal PCB levels in other populations (Halldorsson et al. 2008). Fatty fish contains n-3 polyunsaturated fatty acids (PUFA) that in a randomized controlled trial have been shown to prolong gestation and increase birth weight (Olsen et al. 2007). A study of a representative sample of Danish pregnant women that explicitly addressed competitive effects of n-3 polyunsaturated fatty acids and organochlorine contaminants in seafood did not indicate that the effects on birth weight of the PUFA outweighed possible deleterious effects of PCBs or other contaminant exposures in the study population (Halldorsson et al. 2008). Since the balance of effects is determined by the relative exposure levels, these findings may not apply to populations consuming other types of seafood. Other studies have not observed associations between PCBs and birth weight after adjusting for marine n-3 fatty acids (Grandjean et al. 2001). Accurate information on fish intake was not available in all cohorts. In general, we would expect residual confounding due to non-differential misclassification of fish consumption to bias the association between PCBs and birth weight upward. Therefore it seems unlikely that misclassification would cause the inverse association that we observed. In addition, fish consumption did not appear to contribute to heterogeneity across the cohorts. It is possible, however, that the misclassification might have been related to other sources of error and

possibly to exposure given that it varied among the cohorts such that any resulting bias might differ from expectations.

The PCB congener mixture in human tissues depends on the source of exposure and the time of sampling relative to exposure (Faroon and Olson 2000). Since PCB congeners vary in toxicity, differences in PCB congener profiles across populations may result in differences in effects on birth weight (if any) and explain some of the heterogeneity of the effect estimates. While PCB 153 was highly correlated with the non-dioxin-like PCB 138 and PCB 180 in all cohorts (r values ranging from 0.79 to 0.99), the association with the dioxin like PCB 118 was weaker [r values ranging from 0.23 to 0.83 except in the Faroese [r = 0.94 for FAROES2 and 0.90 for FAROES3, respectively (Grimvall et al. 1997)]. Other biopersistent organochlorines that are correlated with PCB 153, such as dioxins, hexachlorobenzene (Eggesbo et al. 2009), hexachlorocyclohexane, dieldrin and others (Longnecker et al. 2005) may add to the observed heterogeneity. It is not possible to examine possible differential effects of different mixtures of PCB congeners with the available data, but geographical area and calendar time of the study did not contribute to the observed heterogeneity.

Measurements from cord blood reflect exposure at delivery but may not be a good marker of exposure in early pregnancy (Murphy et al 2010) and maternal blood samples taken in late pregnancy (as the majority of samples in this study) may not truly reflect fetal exposure during embryogenesis In a longitudinal study Bloom et al observed substantially lower serum concentrations of PCB congeners six weeks after delivery and in early pregnancy compared to the period before conception (Bloom et al. 2007). The magnitude of change from early to late pregnancy (if any) is, to the best of our knowledge, unknown. Extrapolating fetal exposure from breast milk samples is less reliable, as exposure assessment is retrospective and exposure levels decline with time after delivery because of elimination through breast milk (Redding et al. 2008). On the other hand, results of a recent study suggest that while variable, the average monthly decrease in milk PCB is only 1% (Hooper et al., 2007). Thus, the error in exposure introduced by using concentrations in milk one month after birth as a

surrogate for prenatal exposure may be limited. We were not able to fully address the effects of different sampling times relative to pregnancy, but note that a poor proxy of a causal agent is more likely to result in dilution of risk estimates and therefore foremost is an issue in studies with no associations although non-differential misclassification of exposure not invariably results in bias towards null.

The conversion of concentrations measured from maternal serum and breast milk into those of cord serum was for descriptive purposes only, whereas the meta-analysis was based upon within-population regression estimates of exposures that were measured in a single biological matrix. . We did not attempt to perform exposure-response analyses across the various populations, and thus did not include the absolute values of exposures in the meta-analysis.

The specificity of results indicating associations of birth weight with PCBs but not p,p'-DDE, and demonstration of the expected associations between birth weight and gender, tobacco smoking and body mass index , supports the validity of findings and suggests that the PCB 153 - birth weight association was not merely an artefact of study design or analysis. The correlation between concentrations of PCB 153 and p,p'-.DDE was about 0.6 in most cohorts, but adjustment by p,p'-DDE in the individual cohorts did not attenuate the inverse association between PCB and birth weight and there was no significant interaction between PCB 153 and p,p'-DDE on birth weight within or across cohorts.

Are results biased by reverse causation? Large maternal weight gain is correlated with high birth weight and could reduce POC levels because of dilution, thus producing an artificially negative association between POC concentration and birth weight. The much stronger association of PCB 153 than p,p'-DDE with birth weight is inconsistent with the dilution hypothesis, unless partitioning of PCBs into adipose tissue is greater than for DDE. But available data does not indicate that placental transfer of DDE deviates from PCBs in average (Needham et al. 2011b). Moreover, in cohorts where data on weight gain during pregnancy were available (INMA and PELAGIE), additional analyses adjusting for weight gain during

pregnancy did not change the risk estimates materially. For instance, for the INMA cord subcohort, the weight gain unadjusted risk estimate was -0.30 (95% CI: -0.57; -0.04) and the weight gain adjusted estimate was -0.31 (95% CI: -0.57; -0.05).

The discrepant findings in several earlier studies are puzzling (Fein et al. 1984;Karmaus and Zhu 2004;Murphy et al. 2010;Patandin et al. 1998;Rylander et al. 1995;Rylander et al. 1996;Rylander et al. 1998;Wojtyniak et al. 2010;Sonneborn et al. 2008; Dar et al. 1992;Gladen et al. 2003;Grandjean et al. 2001;Longnecker et al. 2005;Mendez et al. 2010;Vartiainen et al. 1998). Among the populations included in this meta-analysis only four showed a significant inverse association between PCB 153 and birth weight, of which 1-2 might be expected as chance findings at the 5% significance level (15 populations and 2 compounds = 30 comparisons). Reasons may be inadequate sample sizes, exposure misclassification, or exposure profile heterogeneity. However, we acknowledge that more consistent findings in earlier studies and across populations in this study would add to the credibility of the overall result.

Although the possible mode of action for effects of PCBs on birth weight is uncertain, the endocrine disrupting properties of PCBs could be involved. Estrogens play a pivotal role in promoting fetal growth (Kaijser et al. 2000). Both estrogenic and anti-estrogenic activity has been observed for non-dioxin-like-PCBs (NDL-PCBs). A recent study analyzing the toxicity profiles of twenty-four PCB congeners by *in vitro* assays revealed that higher chlorinated NDL-PCBs were weak estrogen receptor (ER) antagonists, and that several NDL-PCBs inhibited estradiol-sulfotransferase activity (Hamers et al 2011). Anti-estrogenic congeners may inhibit fetal growth by their intrinsic activity or by disruption of endogenous estrogen metabolism. In addition, both estrogenic and anti-estrogenic activity has been observed for hydroxylated metabolites of lower chlorinated non-dioxin-like PCBs (Connor et al. 1997), which are transferred more efficiently through placenta than the parent compounds (Park et al 2008). PCBs exhibit also a weak anti androgenic activity, which may also have an impact on fetal growth (Luke et al 2005). Finally, PCBs are also known to interfere with thyroid

hormone status in animals and humans (for reviews see Klaassen and Hood 2001 and Brouwer et al.1998). In vitro assays showed that several NDL-PCBs inhibit estradiol-sulfotransferase activity and bound to transthyretin (Hamers et al, 2011). It is well known that maternal hypothyroidism is related to low birth weight (Blazer et al. 2003).

Low birth weight represents a mix of preterm delivery and reduced fetal growth. Since PCB levels were not associated with duration of gestation in either sex , our results suggest that PCB dose may be related to birth weight restriction rather than preterm delivery. This hypothesis was corroborated by an analysis restricted to infants born at term which showed no material changes in effect estimates, consistent with several recent studies (Halldorsson et al. 2008;Hertz-Picciotto et al. 2005;Longnecker et al. 2001;Sonneborn et al. 2008).

In two studies reduced birth weight has been observed in association with PCBs among boys only (Hertz-Picciotto et al. 2005;Sonneborn et al. 2008). This observation was not corroborated by our analyses. Earlier reports on gender specific effects are not supported by animal or mechanistic evidence and may represent chance findings.

CONCLUSION

Our harmonized meta-analysis of twelve European mother-child cohorts including more than 7,000 pregnancies suggests that low-level PCB exposure (or correlated exposures) impairs fetal growth , while current levels of p,p'-DDE were not associated with birth weight adjusted for gestational age. On average, birth weight declined by 150 g per one µg/L increase in PCB 153 cord serum concentration. The study adds to the mounting evidence that low-level exposure to PCBs is inversely associated with fetal growth.

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Table 1: Description of the ENRIECO/OBELIX birth cohorts with biological PCB 153/p,p'-DDE exposure biomarkers included in the present study

COHORT	SETTING		ENROLLMENT				EXPOSURE ASSESSMENT			N[a]		MAIN REFERENCE
	Locations	Time period	Method	Only babies at term?	Other exclusion criteria	Participation rate	Selection criteria for exposure assessment (if any)	Biological matrix	Time of collection	PCB 153	p,p'-DDE	
GRD	THE NETHERLANDS (Groningen-Rotterdam)	1990-1992	During prenatal consultations in late pregnancy by obstetricians or midwifes	yes	Serious illness during pregnancy; Congenital anomalies; White race; Parity>2; Caesarian section	70%	Availability of biological samples	Cord plasma	At birth	382	-	(Huisman et al. 1995)
	GERMANY (Dusseldorf)	1993-1995	At delivery from the obstetrical wards of three Düsseldorf hospitals by three medical students	yes	Serious illness during pregnancy; Congenital anomalies; Native German families Parity>2; Caesarian section	70%	Availability of biological samples	Cord serum	At birth	141	-	(Walkowiak et al. 2001)
FAROES - cohort 2	THE FAROE ISLANDS	1994-1995	Consecutive births at the National Hospital in Torshavn, but from women living away from the capital area of Torshavn	no	Serious congenital disease	64%	Availability of biological samples	Maternal serum	Week 34 (from antenatal consultation)	173	173	(Steuerwald et al. 2000)
FAROES - cohort 3	THE FAROE ISLANDS	1997-2000	Consecutive pregnant women	no	Serious congenital disease	60%	Breastfeeding	Breast milk	Days 3- 5 and at 2 weeks	596	596	(Weihe et al. 2003)

Table 1 (cont.)

COHORT	SETTING		ENROLLMENT				EXPOSURE ASSESSMENT			N[a]		MAIN REFERENCE
	Locations	Time period	Method	Only babies at term?	Other exclusion criteria	Participation rate	Selection criteria for exposure assessment (if any)	Biological matrix	Time of collection	PCB 153	p,p'-DDE	
INMA	SPAIN (Menorca)	1997-1999	During prenatal care at general practices of the island (in public or private health centres)	no	Maternal age<16y; To have followed any program of assisted reproduction; Not wish to deliver in the reference hospital; Speaking difficulties	98%	Availability of biological samples	Cord serum	At birth	404	405	(Carrizo D et al. 2006)
	SPAIN (Granada)	2000-2002	During hospital admission for delivery in the study area	no	Maternal age<16y; To have followed any program of assisted reproduction; Not wish to deliver in the reference hospital; Speaking difficulties	Unknown	Availability of biological samples	Cord serum	At birth	-	318	(Ribas-Fito et al. 2006)
	SPAIN (Valencia)	2004-2005	During the first prenatal visit in the main public hospital or health centre of the study area	no	Maternal age<16y; To have followed any program of assisted reproduction; Not wish to deliver in the reference hospital; Speaking difficulties	54%	Availability of biological samples	Cord serum	At birth	499	499	(Vizcaino E et al 2010)
	SPAIN (Sabadell)	2004-2006	During the first prenatal visit in the main public hospital or health centre of the study area	no	Maternal age<16y; To have followed any program of assisted reproduction; Not wish to deliver in the reference hospital; Speaking difficulties	60%	Availability of biological samples	Maternal serum	Week 13 of pregnancy	605	605	(Ribas-Fito et al. 2006)
	SPAIN (Asturias)	2004-2007	During the first prenatal visit in the main public hospital or health centre of the study area	no	Maternal age<16y; To have followed any program of assisted reproduction; Not wish to deliver in the reference hospital; Speaking difficulties	45%	Availability of biological samples	Cord serum	At birth	25	25	(Ribas-Fito et al. 2006)
	SPAIN (Gipuzkoa)	2006-2008	During the first prenatal visit in the main public hospital or health centre of the study area	no	Maternal age<16y; To have followed any programme of assisted reproduction; Not wish to deliver in the reference hospital; Speaking difficulties	68%	Availability of biological samples	Maternal and cord serum	Week 13.5 of pregnancy and at birth	604	605	(Ribas-Fito et al. 2006)
DUISBURG	GERMANY (Duisburg)	2000-2002	Self-selected pregnant women within a predefined area mainly in Duisburg South	yes	Non healthy mother-infant pairs; Babies not from German or Turkish speaking families; Apgar score <8; Parity>3	Unknown	Availability of biological samples	Maternal blood	32nd week of pregnancy	189	189	(Wilhelm et al. 2008;Wittsiepe et al. 2008)
FLEHSI	BELGIUM (Flanders)	2002-2004	At delivery in maternities of eight districts covering 20% of Flanders' area	no	Complications in delivery; Living less than 5 years in the area; Not Dutch reading	98%	Availability of biological samples	Cord plasma	At birth	1068	1114	(Koppen et al. 2009)

Table 1 (cont.)

COHORT	SETTING		ENROLLMENT				EXPOSURE ASSESSMENT			N[a]		MAIN REFERENCE
	Locations	Time period	Method	Only babies at term?	Other exclusion criteria	Participation rate	Selection criteria for exposure assessment (if any)	Biological matrix	Time of collection	PCB 153	p,p'-DDE	
INUENDO	GREENLAND	2002-2004	By the local midwife when visiting the local hospital or health clinic from 15 municipallies of all regions in Greenland	no	Maternal age<18y; Not born in the country	90%	Availability of biological samples	Maternal serum	24 weeks on average	546	546	(Toft et al. 2005)
	POLAND (Warsaw)	2003-2004	During antenatal classes at the obstetric outpatient clinic of the Gynaecological and Obstetric Hospital of the Warsaw School of Medicine or with physicians at a collaborating hospital in the same city	no	Maternal age<18y; Not born in the country	68%	Availability of biological samples	Maternal serum	33 weeks on average	199	199	(Toft et al. 2005)
	UKRAINE (Kharkiv)	2003-2004	During visit of one of eight antenatal clinics or three maternity hospitals in Kharkiv by gynecologists	no	Maternal age<18y; Not born in the country	26%	Availability of biological samples	Maternal serum	24 weeks on average	589	589	(Toft et al. 2005)
Michalovce	SLOVAKIA	2002-2004	At delivery in maternities of two districts, one with high contamination of PCBs (Michalovce), and another one upwind and upstream of the chemical facility with lower contamination levels (Svidnik).	no	Mothers with major illness; Severe congenital anomalies; Maternal age<18y; Living less than 5 years in the area; Parity>4	60%	Availability of biological samples	Cord serum	At birth	1082	1082	(Hertz-Picciotto et al. 2003)
HUMIS	NORWAY	2002-2006	Two-four weeks after birth during the routine health visit at home	no	Non-fluent in Norwegian	64%	Random selection in the cohort; Breastfeeding	Breast milk	Milk sampled on eight consecutive days and pooled.	418	418	(Eggesbo et al. 2009)
PELAGIE	FRANCE (Brittany)	2002-2006	During first prenatal visit by gynecologists or obstetricians in the study area	no	Inclusion later than 19 weeks of pregnancy	80%	Stratified random selection of a subcohort among the live born cohort; Availability of biological samples	Cord serum	At birth	396	395	(Petit et al. 2010)
ELFE pilot	FRANCE	2007	At delivery in maternities	no	Maternal age<18y; Not French speaking; Parity >2	55%	Breastfeeding	Breast milk	One month after birth	44	-	(Vandentorren et al. 2009)
RHEA	GREECE (Heraklion, Crete)	2007-2008	Contact by interviewer of all pregnant women living in Heraklion around 12 weeks of gestation	no	Maternal age<18y; Insufficient understanding of the Greek language	72%	Random selection of a small subcohort	Maternal serum	During the first interview	30	30	(Vardavas et al. 2010)

[a] Number of liveborn singleton births with exposure levels

Table 2: Concentration of exposure biomarkers PCB 153 and p,p'-DDE (ng/L) in cord serum, actual or obtained by conversion, of the ENRIECO/OBELIX birth cohorts

	PCB 153 (ng/L)					p,p'-DDE (ng/L)				
Cohort	N	mean	std	median	N<LOD/LOQ	N	mean	std	median	N<LOD/LOQ
GRD*	523	170.6	99.7	150.0	0	-	-	-	-	-
FAROES2**	167	648.4	580.0	484.2	2 (1.2%)	167	1708.3	1433.9	1208.0	0
FAROES3***	549	434.4	347.6	345.6	0	549	987.7	994.9	729.6	0
INMA cord*	1227	156.1	112.7	134.1	114 (9.3%)	1515	1380	2269.8	596.0	57 (3.8%)
INMA mat**	856	52.8	34.7	46.4	56 (6.5%)	857	262.6	1030.0	131.2	5 (0.6%)
DUISBURG**	189	147.1	99.4	124.0	0	189	323.7	435.6	216.0	0
FLEHSI*	1015	73.3	56.7	60.0	202 (19.9%)	1061	315.6	344.6	220.0	19 (1.8%)
Greenland**	546	253.8	341.9	155.1	7 (1.3%)	546	634.6	684.2	435.7	10 (1.8%)
Warsaw**	199	23.8	17.8	20.1	43 (21.6%)	199	824.7	518.3	668.8	0
Kharkiv**	577	45.8	36.3	37.1	20 (3.5%)	577	1100.8	762.3	916.3	0
Michalovce*	1036	393.5	458.3	271.8	2 (0.2%)	1036	1329.5	1338.4	1014.7	8 (0.8%)
HUMIS***	409	43.1	20.0	39.2	0	409	75.0	111.0	49.8	0
PELAGIE*	396	126.1	77.7	110.0	2 (0.5%)	395	253.3	335.8	180.0	76 (19.2%)
ELFE pilot***	43	100.4	52.7	92.5	0	-	-	-	-	-
RHEA**	30	28.0	13.4	23.8	0	30	573.2	389.2	496.0	0
Combined	7762	179.8	156.6	139.6	448 (5.8%)	7530	751.5	819.1	527.9	175 (2.3%)

LOD = limit of detection; LOQ = limit of quantification.

Observed cord serum concentrations* and estimated cord serum concentrations based on measured concentrations in maternal serum (whole blood for Duisburg)** or breast milk*** (see Supplemental Material, pages 2-3 for additional information on conversions).

Figure Legends

Figure 1**:** Adjusted regression coefficients (95% CI) of cord serum PCB 153 (ng/L) with birth weight (grams). The squares are proportional to the inverse variance of the effect estimation of each cohort.

Footnote: Covariates included in the regression model: child's gestational age and gender, mother's region, maternal BMI, height, smoking status during pregnancy, socioeconomic status, mother's age, parity, ethnicity and time of sampling.

Figure 2: Adjusted regression coefficients (95% CI) of cord serum p,p'-DDE (ng/L) with birth weight (grams). The squares are proportional to the inverse variance of the effect estimation of each cohort.

Footnote: For model covariates, see legend to Figure 1

Figure 1

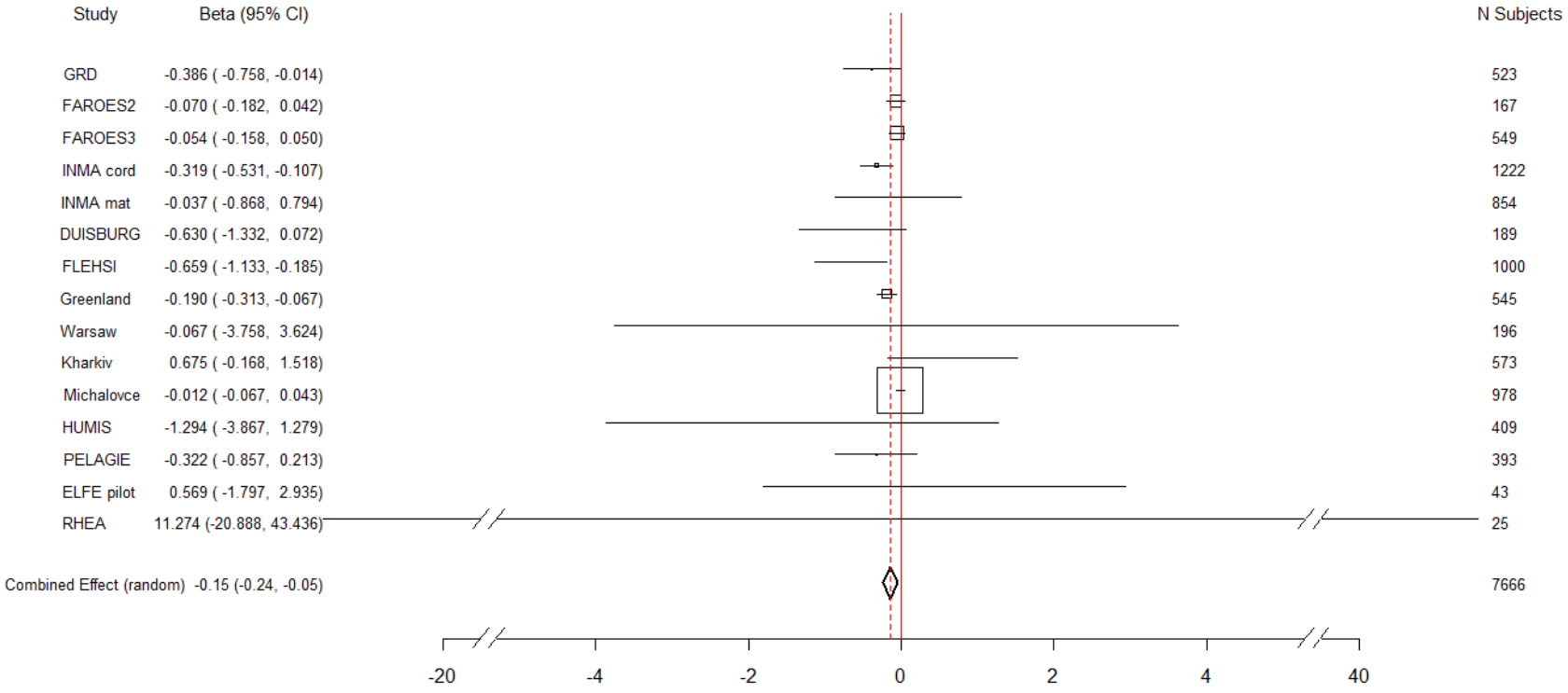
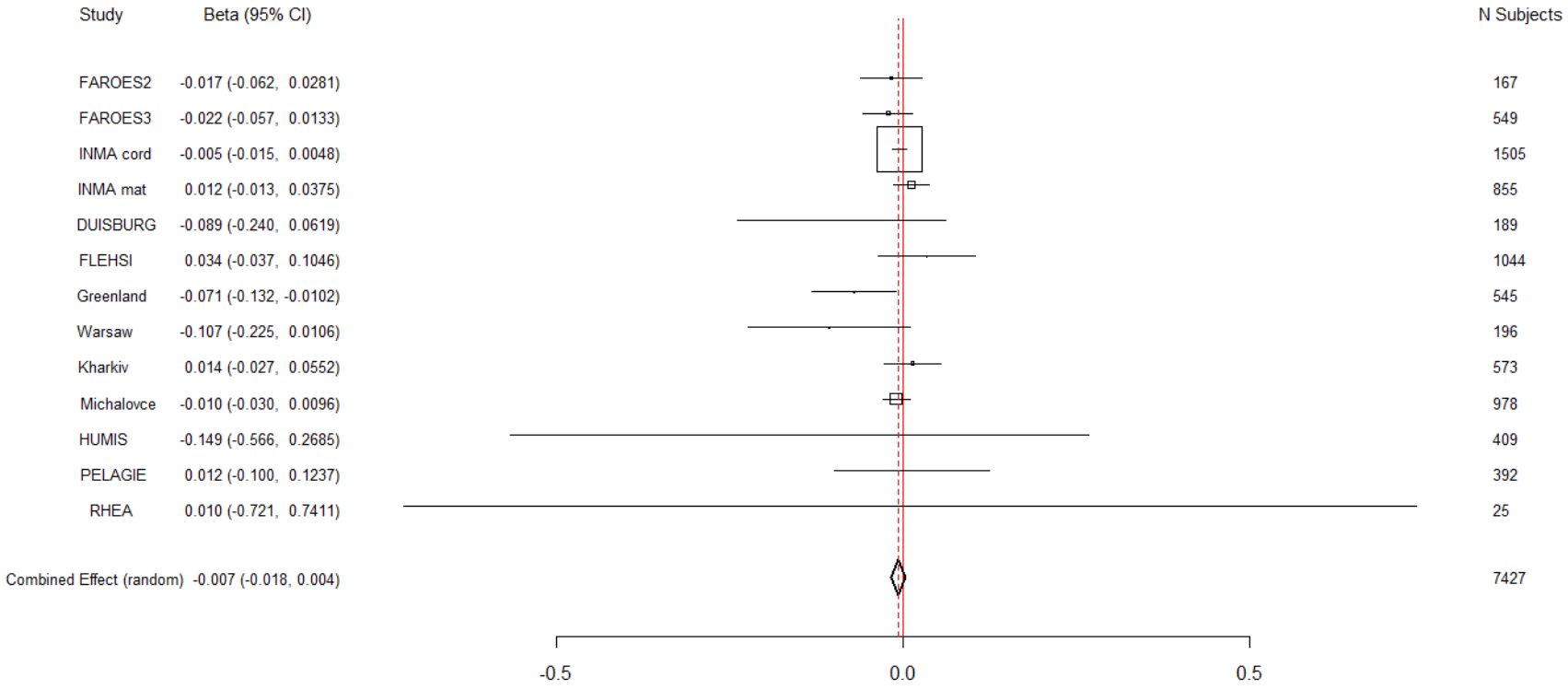

Study
Beta (95% CI)
N Subjects
GRD -0.386 (-0.758, -0.014) 523
FAROES2 -0.070 (-0.182, 0.042) 167
FAROES3 -0.054 (-0.158, 0.050) 549
INMA cord -0.319 (-0.531, -0.107) 1222
INMA mat -0.037 (-0.868, 0.794) 854
DUISBURG -0.630 (-1.332, 0.072) 189
FLEHSI -0.659 (-1.133, -0.185) 1000
Greenland -0.190 (-0.313, -0.067) 545
Warsaw -0.067 (-3.758, 3.624) 196
Kharkiv 0.675 (-0.168, 1.518) 573
Michalovce -0.012 (-0.067, 0.043) 978
HUMIS -1.294 (-3.867, 1.279) 409
PELAGIE -0.322 (-0.857, 0.213) 393
ELFE pilot 0.569 (-1.797, 2.935) 43
RHEA 11.274 (-20.888, 43.436) 25
Combined Effect (random) -0.15 (-0.24, -0.05) 7666
-20
-4
-2
0
2
4
40

Figure 2.


Study
Beta (95% CI)
N Subjects
FAROES2 -0.017 (-0.062, 0.0281) 167
FAROES3 -0.022 (-0.057, 0.0133) 549
INMA cord -0.005 (-0.015, 0.0048) 1505
INMA mat 0.012 (-0.013, 0.0375) 855
DUISBURG -0.089 (-0.240, 0.0619) 189
FLEHSI 0.034 (-0.037, 0.1046) 1044
Greenland -0.071 (-0.132, -0.0102) 545
Warsaw -0.107 (-0.225, 0.0106) 196
Kharkiv 0.014 (-0.027, 0.0552) 573
Michalovce -0.010 (-0.030, 0.0096) 978
HUMIS -0.149 (-0.566, 0.2685) 409
PELAGIE 0.012 (-0.100, 0.1237) 392
RHEA 0.010 (-0.721, 0.7411) 25
Combined Effect (random) -0.007 (-0.018, 0.004) 7427
-0.5
0.0
0.5